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Comparative Effects of Losartan and Enalapril on Exercise Capacity and Clinical Status in Patients With Heart Failure

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Objectives. **This study was designed to determine 1) whether 12-week oral administration of losartan, an angiotensin II receptor antagonist, in patients with heart failure is well tolerated; and 2) whether functional capacity and clinical status of patients with heart failure in whom treatment with an angiotensin-converting enzyme (ACE) inhibitor is replaced with losartan for 12 weeks will remain similar to that noted in patients in whom treatment with an ACE inhibitor is continued.**

Background. **Losartan is a specific, nonpeptide angiotensin II receptor antagonist. Although specific receptor blockade with losartan has certain theoretic advantages over nonspecific ACE inhibition, definitive demonstration of comparable effects in patients with congestive heart failure is lacking.**

Methods. **A double-blind, multicenter, randomized, parallel, enalapril-controlled study was conducted in 116 patients with congestive heart failure (New York Heart Association functional classes II to IV) and left ventricular ejection fraction ≤45% previously treated with stable doses of ACE inhibitors and diuretic agents, with or without concurrent digitalis and other vasodilators. After a baseline exercise period, open-label ACE inhibitors were discontinued, and patients were randomly assigned to 12 weeks of therapy with losartan, 25 mg/day (n = 38); losartan, 50 mg/day (n = 40); or enalapril, 20 mg/day (n = 38). Drug efficacy was evaluated by changes in maximal treadmill exercise time (using a modified Naughton protocol), 6-min walk test, left ventricular ejection fraction and dyspnea-fatigue index. Safety was measured by the incidence of clinical and laboratory adverse experiences.**

Results. **The treadmill exercise time and the 6-min walk test did not change significantly after replacement of ACE inhibitor therapy with losartan. Similarly, a significant change was not observed in either the dyspnea-fatigue index or left ventricular ejection fraction at the end of double-blind period relative to baseline.**

Conclusions. **Losartan was generally well tolerated and comparable to enalapril in terms of exercise tolerance in this short-term (12-week) study of patients with heart failure. The clinical effects of long-term angiotensin II receptor blockade compared with ACE inhibition remain to be studied.**

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Pharmacologic blockade of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme (ACE) inhibitors in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction results in clinical benefits such as symptomatic relief of dyspnea, improvement in left ventricular function, prevention of progressive ventricular dilation, decreased need for hospitalization and improved survival (1–6).

Recently, hemodynamic benefits accompanied by favorable clinical responses have been reported using an alternative method of inhibition of the RAAS with the angiotensin II receptor antagonist losartan (7–11). Specific blockade of the angiotensin II receptor has certain theoretic advantages over nonspecific ACE inhibition (12). For example, losartan does not block the degradation of vasoactive substances such as bradykinin, enkephalins and substance P, and may not cause side effects such as cough related to ACE inhibitor–induced bradykinin accumulation. In addition, specific angiotensin II receptor blockade could block the deleterious effects of angiotensin II produced not only through the classic pathway involving ACE but also by nonconverting enzyme-dependent pathways, which are not blocked by ACE inhibitors, within cardiac myocites and arterial wall tissues. For these reasons, blockade of the actions of angiotensin II at the receptor level

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
LVEF = left ventricular ejection fraction
RAAS = renin-angiotensin-aldosterone system

may constitute an attractive pharmacologic alternative for all patients with heart failure, not just for patients intolerant to the side effects of ACE inhibitors (13–15). Before long-term clinical studies using losartan can be initiated, additional information on its safety profile and effectiveness are required. Accordingly, this study was designed to determine 1) whether 12-week oral administration of losartan to patients with heart failure is well tolerated; and 2) whether the functional capacity and clinical status of patients with heart failure in whom treatment with an ACE inhibitor is replaced with losartan for 12 weeks will remain similar to that noted in patients in whom treatment with the ACE inhibitor is continued.

Methods

Study design. This study was a multicenter (16 centers—15 from the United States and 1 from Canada), double-blind, randomized, parallel, enalapril-controlled study performed in 116 patients with symptomatic heart failure (New York Heart Association functional classes II to IV) and left ventricular ejection fraction (LVEF) ≤45%.

Baseline exercise period: screening and eligibility. Figure 1 depicts the protocol used for data acquisition. At the initial clinic visit, patients underwent a medical history review, a complete physical examination, a review of symptoms of heart failure, a complete laboratory screening, a radionuclide ventriculogram, a 12-lead electrocardiogram, a chest x-ray film and the dyspnea-fatigue index (16). Patients eligible to participate in the study must have received stable doses of ACE inhibitors and diuretic agents for a minimum of 6 and 2 weeks, respectively, before the first baseline exercise test (visit 2). Therapy with digoxin or non-ACE inhibitor vasodilators, or both, was permitted; if receiving digoxin, the patient had to be treated with digoxin for 6 weeks before the second study visit, and the dosage had to remain stable for the last 2 weeks; if receiving non-ACE inhibitor vasodilators, the patient had to be taking stable doses for 6 weeks before visit 2. Before enrollment all patients signed an informed consent form, which was previously approved by the Institutional Review Board of each institution.

Placebo study medication was given to all patients during the baseline period starting at visit 2. During this period, patients continued to receive ACE inhibitors. All clinic visits were conducted in the morning, before the study drug or other concomitant medications were taken (i.e., at the trough of the dose interval for all study and nonstudy cardiovascular medications). At each visit, the patient underwent an abbreviated physical examination and a review of symptoms. In addition, a complete laboratory screening and dyspnea-fatigue index were also performed during visit 4. Three 6-min walk tests, at visits 2, 3, and 4, and two treadmill exercise tests using the modified Naughton protocol, at visits 2 and 3, were performed during the baseline exercise period. During these visits, the treadmill exercise tests were always performed at least 1 h or more after the 6-min walk test.

Patients were randomized as either a "treadmill" or "non-treadmill patient"; at least 80% of patients enrolled in each center had to be treadmill patients. To qualify as a "treadmill patient," subjects had to successfully complete two consecutive baseline treadmill exercise tests in which the exercise duration did not differ by more than 10% (if the exercise duration was <10 min for the first test) or 60 s (if the exercise duration was >10 min for the first test). To satisfy this inclusion criterion, treadmill tests could be repeated a maximum of five times during the baseline period. Patients were scheduled with intervals ranging from 2 days to 2 weeks between exercise tests.

Randomization and double-blind period. Randomization into the double-blind period occurred within 5 days of completion of the baseline exercise period. At the time of randomization, open-label ACE inhibitor therapy was discontinued. All other concomitant medications administered during the baseline exercise period were continued during the double-blind period. Double-blind study medication was initiated in the morning before the patient received any other concomitant

	BASELINE EXERCISE PERIOD				DOUBLE BLIND PERIOD						
	Visit 1 (Screening)	Visit 2	Visit 3	Visit 4	WK 1	WK 2	WK 4	WK 6	WK 9	WK 11	WK 12
Physical Exam	X	X	X	X	X	X	X	X	X	X	X
Laboratory Screen	X			X	X	X	X	X			X
RNA (EF)	X										X
Dyspnea-Fatigue Index	X			X				X			X
Six-Minute Walk Test		X	X	X				X	X		X
Treadmill Exercise Test		X	X					X		X	X

Start with Placebo Medication ↑ ↑ Randomization

Figure 1. Protocol and data acquisition. EF = ejection fraction; RNA = radionuclide angiography.

medications. Patients were randomized to receive one of three active treatments for 12 weeks: 1) losartan, 12.5 mg, titrated as tolerated to 25 mg every day; 2) losartan, 12.5 mg, titrated as tolerated to 25 and then 50 mg every day; or 3) enalapril, 2.5 mg, titrated as tolerated to 5 and then 10 mg twice daily.

In all study groups, dosages were increased at 1-week intervals unless a serious or intolerable adverse experience occurred.

Evaluation criteria. Efficacy variables included symptom-limited treadmill exercise duration (6, 11 and 12 weeks after randomization), 6-min walk test (6, 9 and 12 weeks after randomization) (17), the dyspnea-fatigue index (6 and 12 weeks after randomization) (16), signs and symptoms of heart failure and functional class. The average duration of both qualifying baseline treadmill exercise tests and the average distance of the final two baseline 6-min walk tests were used as baseline exercise duration and distance, respectively. The week 12 treadmill exercise duration (in seconds) was calculated as the average of week 11 and week 12 data when the difference in days between the two tests was ≤14 days; if this interval was larger, only the week 12 measurement was used. Other measurements performed at each study visit are outlined in Figure 1. Safety and tolerability were assessed by the incidence of clinical and laboratory adverse events.

Statistics. *Baseline comparisons.* Several statistical methods were used to compare the three different treatment groups with respect to the distribution of baseline patient characteristics. The Fisher exact test was used to compare the treatment groups with respect to the distribution of nominal demographic characteristics and race. The Wilcoxon test was used to compare treatment groups with respect to ordinal categoric attributes such as functional class. Analysis of variance (based on ranks) was used to compare treatment groups with respect to continuous (ordinal) attributes such as walk distance, exercise duration, dyspnea-fatigue index, jugular venous distention at 45° and ejection fraction.

Efficacy analyses approaches and methods. Analyses were performed using the baseline and last double-blind measurements. If a patient's week 12 data were missing, measurements obtained during the last completed double-blind period were used for the statistical analysis. Analyses were performed for both continuous and discrete end points. Intergroup comparisons with respect to continuous end points (walk distance, exercise duration, dyspnea-fatigue index, ejection fraction and jugular venous distention at 45°) were based on adjusted means resulting from analysis of covariance performed on the change from baseline with treatment as a factor, baseline as a covariate and investigator as a blocking variable. With regard to the discrete end points (exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, edema, rales, third heart sound and functional class), baseline-adjusted comparisons between the treatment groups were performed using Cochran-Mantel Haenszel statistics. Intragroup changes from baseline were analyzed using the Wilcoxon signed-rank test.

Results

Patient characteristics. Baseline patient demographics and heart failure characteristics are summarized in Table 1. The majority of patients were male (78%) and white (71%). The mean age was 58 ± 13 years (range 25 to 83); the mean duration of the diagnosis of heart failure was 4.4 ± 4.8 years (range 0.33 to 35); and the mean LVEF was 25 ± 7%. Most of the patients were identified as being in functional class II (47%) or III (51%) and diagnosed with ischemic heart disease (47%) or dilated cardiomyopathy (41%). There were no statistically significant differences in the demographics and heart failure characteristics among the different treatment groups. The most common therapies used before enrollment are displayed in Table 2. As noted, all patients were receiving some type of cardiovascular medications, with 99% of the patients receiving diuretic agents, 84% digoxin, 43% enalapril and 37% captopril.

Efficacy. Several criteria were used to assess the efficacy of treatment with losartan. These included 1) a 6-min walk test; 2) a modified Naughton treadmill exercise test; 3) the dyspnea-fatigue index; 4) the LVEF; and 5) signs and symptoms of heart failure. The effects of treatment assignment on each of these variables are shown in Table 3.

Six-minute walk test. No intergroup differences in mean change in distance walked were observed ($p = 0.79$).

Modified Naughton treadmill exercise test. No intergroup differences were noted at baseline. Exercise duration at the end of the study was increased from baseline for the enalapril group ($p = 0.03$) and marginally increased ($p = 0.06$) for the 50-mg losartan group.

Dyspnea-fatigue index. No significant intergroup differences were detected at baseline ($p = 0.92$). At the end of the study, this index was significantly improved from the baseline value for the 25-mg losartan group only ($p = 0.03$).

Ejection fraction. No differences in mean change in LVEF were observed among the different treatment groups ($p = 0.75$). The LVEF at week 12 was significantly different from that at baseline in the 50-mg losartan group only ($p = 0.02$).

Signs and symptoms of heart failure. The clinical status of each patient was assessed with regard to dyspnea, paroxysmal nocturnal dyspnea, orthopnea, jugular venous pressure, peripheral edema, pulmonary rales, third heart sound and functional class. As shown in Table 4, no statistically significant differences among the treatment groups were observed in the distribution of patients with regard to any of these variables. Functional class improved in 19 patients (16%), evenly distributed among the treatment groups. Table 4 shows the incidence of worsening of the signs and symptoms of heart failure at the end of the double-blind period. No statistically significant differences were noted among the treatment groups in the proportion of patients (25 mg of losartan, n = 5 [13.2%]; 50 mg of losartan, n = 3 [7.5%]; 20 mg of enalapril, n = 2 [5.3%]) satisfying the prospective definition of worsening heart failure.

Subgroup analyses were performed based on age, gender, race, LVEF and functional class. The effect of each of these

Table 1. Baseline Patient Characteristics

	L25 (n = 38)	L50 (n = 40)	E20 (n = 38)	Total (n = 116)
Gender				
Female	6 (16%)	11 (28%)	9 (24%)	26 (22%)
Male	32 (84%)	29 (73%)	29 (76%)	90 (78%)
Age (yr)				
Mean ± SD	57.4 ± 11.3	56.3 ± 16.2	59.7 ± 11.5	57.8 ± 13.2
Range	(28–80)	(25–83)	(33–81)	(25–83)
Racial origin				
White	27 (71%)	26 (65%)	29 (76%)	82 (71%)
Oriental	1 (3%)	1 (3%)	1 (3%)	3 (3%)
Black	9 (24%)	11 (28%)	5 (13%)	25 (22%)
Hispanic	1 (3%)	2 (5%)	3 (8%)	6 (5%)
Duration of primary diagnosis (yr)				
<1	11 (29%)	4 (10%)	8 (21%)	23 (20%)
1–5	18 (47%)	25 (63%)	16 (42%)	59 (51%)
5.01–10	7 (18%)	5 (13%)	8 (21%)	20 (17%)
>10	2 (5%)	6 (15%)	6 (16%)	14 (12%)
Mean ± SD	3.4 ± 3.2	4.5 ± 4.4	5.3 ± 6.2	4.4 ± 4.8
Range	0.33–13	0.5–20	0.33–35	0.33–35
Etiology of heart failure				
Ischemic heart disease	18 (47%)	19 (48%)	18 (47%)	55 (47%)
Dilated cardiomyopathy	13 (34%)	16 (40%)	19 (50%)	48 (41%)
Arterial hypertension	4 (11%)	1 (3%)	0	5 (4%)
Valvular heart disease	2 (5%)	1 (3%)	1 (3%)	4 (3%)
Ischemic cardiomyopathy	0	1 (3%)	0	1 (1%)
Idiopathic etiology	0	1 (3%)	0	1 (1%)
Alcoholic cardiomyopathy	0	1 (3%)	0	1 (1%)
Ethanol abuse	1 (3%)	0	0	1 (1%)
NYHA functional class				
II	20 (53%)	22 (55%)	13 (34%)	55 (47%)
III	18 (47%)	16 (40%)	25 (66%)	59 (51%)
IV	0	2 (5%)	0	2 (2%)

There were no statistically significant differences among the treatment groups. L25 = losartan, 25 mg; L50 = losartan, 50 mg; E20 = enalapril, 20 mg; NYHA = New York Heart Association.

factors on walk distance and treadmill exercise duration was evaluated by performing an analysis of covariance with treatment, investigator and subgroup as factors and baseline walk distance or treadmill exercise duration as a covariate. No treatment by subgroup interactions were significant for any of the subgroups considered.

Table 2. Previous Cardiovascular Therapies by Drug Class*

	L25 (n = 38)	L50 (n = 40)	E20 (n = 38)
ACE inhibitors	38 (100.0)	40 (100.0)	38 (100.0)
Antiarrhythmic agents	4 (10.5)	9 (22.5)	8 (21.1)
Anticoagulant agents†	24 (63.2)	27 (67.5)	23 (60.5)
Beta-blockers	4 (10.5)	1 (2.5)	3 (7.9)
Calcium channel blockers	1 (2.6)	4 (10.0)	3 (7.9)
Digitalis	31 (81.6)	34 (85.0)	33 (86.8)
Diuretic agents	38 (100.0)	40 (100.0)	37 (97.4)
Other vasodilators	13‡ (34.2)	22 (55.0)	23 (60.5)

*This table contains counts of patients. If a patient had multiple concomitant therapies within a particular therapy group, the patient was only counted once in the therapy group total. †Aspirin is included in the category of anticoagulant agents. The number of patients taking aspirin was 33. ‡Statistically significant difference between the 25-mg losartan and 20-mg enalapril groups, $p < 0.05$. Data are presented as number (%) of patients. ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

Safety and tolerance. The safety profile of losartan was evaluated in terms of the incidence of clinical and laboratory adverse experiences. Adverse clinical experiences led to discontinuation of the trial in only one patient from each of the treatment groups. Clinical adverse experiences were reported in 25 patients of the 25-mg losartan group (65.8%); in 27 (67.5%) of the 50-mg losartan group and in 23 (60.5%) of the 20-mg enalapril group. The most common adverse clinical experiences reported were dyspnea, worsening heart failure, dizziness and infection of the upper respiratory tract. A total of six deaths were reported during the double-blind period of the study. One death (due to ventricular tachycardia) occurred in the 25-mg losartan group, whereas five deaths (one death each due to sudden death, worsening heart failure, ventricular arrhythmia and septicemia and one death of unknown cause) were reported in the 50-mg losartan group. There were no deaths reported in the enalapril group. None of these deaths were considered related to study drug therapy.

Table 3. Results of Variables Used to Assess Efficacy of Treatment

Results	Drug	Baseline	Treatment	Change	Mean Change	p Values: Intergroup Comparison: Versus Group B	p Values: Intergroup Comparison: Versus Group C	p Values: Intragroup Comparisons
Walk test (m)	L25 (A)	383 ± 75	393 ± 101	9 ± 48	2.3%	0.69	0.50	0.07
	L50 (B)	394 ± 71	397 ± 102	3 ± 71	0.7%	—	0.78	0.73
	E20 (C)	393 ± 79	393 ± 101	0 ± 63	0%	—	—	0.74
			Intergroup test results for change 0.79					
Treadmill test (s)	L25 (A)	560 ± 151	597 ± 192	37 ± 135	6.6%	0.96	0.65	0.28
	L50 (B)	547 ± 155	584 ± 206	37 ± 119	6.7%	—	0.60	0.06
	E20 (C)	519 ± 179	568 ± 198	49 ± 123	9.4%	—	—	0.03
			Intergroup test results for change 0.85					
Dyspnea fatigue index	L25 (A)	6.2 ± 2.3	6.6 ± 2.2	0.4 ± 1.5		0.94	0.75	0.03
	L50 (B)	6.1 ± 2.4	6.4 ± 2.6	0.3 ± 1.7		—	0.70	1.00
	E20 (C)	5.8 ± 2.3	6.3 ± 2.4	0.5 ± 1.7		—	—	0.30
			Intergroup test results for change 0.92					
LVEF (%)	L25 (A)	26.4 ± 10.1	28.2 ± 12.0	1.8 ± 7.2		0.60	0.86	0.51
	L50 (B)	25.4 ± 10.7	27.7 ± 11.4	2.3 ± 4.4		—	0.47	0.02
	E20 (C)	24.6 ± 7.9	26.1 ± 10.2	1.5 ± 6.8		—	—	0.17
			Intergroup test results for change 0.75					
JVD at 45°	L25 (A)	4.3 ± 4.3	3.9 ± 3.9	−0.3 ± 2.2		0.25	0.59	0.29
	L50 (B)	3.2 ± 3.9	3.9 ± 5.7	0.7 ± 4.1		—	0.53	1.00
	E20 (C)	3.5 ± 3.9	3.7 ± 4.1	0.2 ± 1.9		—	—	0.29
			Intergroup test results for change 0.52					

Data are presented as mean value ± SD. JVD = jugular venous distention; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

Sixteen percent (6 of 38) of the patients in the 25-mg losartan group, 25% (10 of 40) of those in the 50-mg losartan group and 11% (4 of 37) of those in the enalapril group had at least one laboratory adverse experience. Eight percent (3 of 38) of the patients in the 25-mg losartan group, 10% (4 of 40) in the 50-mg losartan group and 5% (2 of 37) of those in the enalapril group had a laboratory adverse experience that was considered drug related.

Laboratory screening (Table 5) revealed no significant intragroup or intergroup differences at 12 weeks for blood urea nitrogen, serum potassium, serum sodium or serum uric acid. The mean changes in serum creatinine were negligible in both losartan groups, whereas the increase from baseline of 0.08 ± 0.15 mg/dl in the enalapril group was significant ($p < 0.05$); this increase was also significant against the 50-mg losartan change (−0.02 mg/dl).

Discussion

The present study was designed to test the following hypotheses: 1) 12-week oral administration of losartan, an angiotensin II receptor antagonist, to patients with heart failure will be well tolerated; and 2) functional capacity and clinical status will be similar in patients with heart failure after oral administration for 12 weeks of either losartan or enalapril. In addition, this study was designed to gain experience in the conversion of therapy from an ACE inhibitor to losartan.

Interpreting the results of the current study. There were no significant differences in the demographics and heart failure characteristics among the different treatment groups at baseline. All patients were withdrawn from ACE inhibitor therapy at the initiation of active study therapy, and most patients were titrated to their expected dose level in each treatment group.

The major variables evaluated as indicators of treatment efficacy were functional capacity and clinical status assessed by treadmill exercise time, 6-min walk test distance, dyspnea-fatigue index, LVEF, signs and symptoms of heart failure and functional class. Because the patients in this study had been previously treated with an ACE inhibitor, exercise capacity was not expected to change significantly during the study, unless treatment with losartan was not effective. The data revealed that exercise duration at the end of the study was increased from baseline in all treatment groups. This increase was significant in the enalapril group ($p = 0.03$) and marginally significant in the 50-mg losartan group ($p = 0.06$). However, the increases in exercise duration were small and not significantly different among the treatment groups. The distance traversed in the 6-min walk test was also not significantly different among any of the treatment groups. Thus, exercise capacity appeared to be similar in patients treated with either 25 mg of losartan once daily, 50 mg of losartan once daily or 10 mg of enalapril twice daily for 12 weeks after discontinuation of open-label ACE inhibitors.

Consistent with the exercise results, the dyspnea-fatigue index and LVEF measurements showed no differences in mean changes among the treatment groups. Although there were no differences in mean changes among treatment groups, there was a significant improvement in the dyspnea-fatigue index in

Table 4. Clinical Status Assessment at End of Study

		Treatment Effect			Comparison (p values)	
Clinical Assessment	Group	Worse	No Change	Improvement	Versus Group B	Versus Group C
Exertional dyspnea	L25 (A)	3 (7.8%)	24 (63.1%)	11 (28.9%)	0.96	0.94
	L50 (B)	4 (10.0%)	25 (62.5%)	11 (27.5%)	—	0.862
	E20 (C)	3 (7.8%)	24 (63.1%)	11 (28.9%)	—	—
Paroxysmal nocturnal dyspnea	L25 (A)	0 (0.0%)	36 (94.7%)	2 (5.2%)	0.88	0.46
	L50 (B)	1 (2.5%)	34 (85.0%)	5 (12.5%)	—	0.41
	E20 (C)	1 (2.6%)	35 (92.1%)	2 (5.2%)	—	—
Orthopnea	L25 (A)	6 (15.7%)	28 (73.6%)	4 (10.5%)	0.95	0.42
	L50 (B)	4 (10.0%)	31 (77.5%)	5 (12.5%)	—	0.24
	E20 (C)	2 (5.2%)	32 (84.2%)	4 (10.5%)	—	—
Edema	L25 (A)	3 (7.8%)	28 (73.6%)	7 (18.4%)	0.10	0.75
	L50 (B)	6 (15.0%)	30 (75.0%)	4 (10.0%)	—	0.21
	E20 (C)	2 (5.2%)	32 (84.2%)	4 (10.5%)	—	—
Rales	L25 (A)	0 (0.0%)	37 (97.3%)	1 (2.6%)	0.12	*
	L50 (B)	2 (5.0%)	37 (92.5%)	1 (2.5%)	—	0.16
	E20 (C)	0 (0.0%)	38 (100%)	0 (0.0%)	—	—
Third heart sound	L25 (A)	3 (7.8%)	31 (81.5%)	4 (10.5%)	0.87	0.41
	L50 (B)	2 (5.0%)	33 (82.5%)	5 (12.5%)	—	0.21
	E20 (C)	2 (5.2%)	35 (92.1%)	1 (2.6%)	—	—
NYHA functional class	L25 (A)	2 (5.2%)	30 (78.9%)	6 (15.7%)	0.99	0.87
	L50 (B)	0 (0.0%)	34 (85.0%)	6 (15.0%)	—	0.84
	E20 (C)	2 (5.2%)	29 (76.3%)	7 (18.4%)	—	—

*Value could not be computed because the covariance matrix is singular. Data are presented as number (%) of patients. Abbreviations as in Table 1.

the 25-mg losartan treatment group ($p = 0.03$) and a significant improvement in ejection fraction in the 50-mg losartan treatment group ($p = 0.02$) when compared with baseline. No statistically significant intergroup differences were observed in the signs and symptoms of heart failure with regard to the distribution of the patients at the end of the double-blind period.

Table 5. Laboratory Results in Three Treatment Groups

	L25 (n = 35*)	L50 (n = 35*)	E20 (n = 35*)
Serum creatinine (mg/dl)			
Baseline values	1.25 ± 0.25	1.24 ± 0.33	1.30 ± 0.37
Change at 12 weeks	0.02 ± 0.14	0.02 ± 0.28†	0.08 ± 0.15‡
Blood urea nitrogen			
Baseline values	19.8 ± 7.2	17.6 ± 6.6	22.1 ± 10.3
Change at 12 weeks	−0.5 ± 5.1	1.1 ± 7.4	3.5 ± 9.2
Serum potassium (mEq/liter)			
Baseline values	4.38 ± 0.44	4.25 ± 0.48	4.44 ± 0.47
Change at 12 weeks	−0.16 ± 0.43	0.12 ± 0.42	−0.05 ± 0.47
Serum sodium (mEq/liter)			
Baseline values	138.7 ± 2.9	139.0 ± 2.7	138.1 ± 2.9
Change at 12 weeks	1.2 ± 5.3	0.2 ± 3.0	−0.3 ± 3.6
Serum uric acid (mg/dl)			
Baseline values	7.45 ± 1.59	7.33 ± 1.91	7.37 ± 2.31
Change at 12 weeks	−0.17 ± 1.68	−0.03 ± 0.97	0.06 ± 1.09

*Minimal sample size for each variable. †Statistically significant difference compared with 20-mg enalapril group, $p < 0.05$. ‡Statistically significant within-group difference, $p < 0.05$. Data are presented as mean value ± SD. Abbreviations as in Table 1.

With respect to safety, a comparable incidence of overall clinical adverse experiences, serious adverse experiences, hypotension-related symptoms and worsening heart failure was observed among all the treatment groups. Unexpectedly, five deaths occurred in the 50-mg losartan treatment group compared with one and none in the 25-mg losartan and 20-mg enalapril treatment groups, respectively. Of these five deaths in the 50-mg losartan treatment group, one occurred as a result of cholecystitis and sepsis and another occurred in a noncompliant patient who apparently had not been taking losartan for 11 days before death, based on the amount of study drug found in the patient's body after death. Hence, three deaths remain unexplained. None of these deaths were considered by the treating physician to be related to study drug therapy. The apparent increase in mortality in the 50-mg losartan group in this study may be a result of chance related to the use of multiple treatment groups with a small sample size, because such an increase in mortality was not observed in the 25-mg losartan group in this study and was not observed after losartan treatment in two other studies in patients with heart failure. In the hemodynamic study reported by Crozier et al. (10), 29, 22 and 26 patients with symptomatic heart failure and baseline pulmonary capillary wedge pressure ≥13 mm Hg received 25 mg of losartan, 50 mg of losartan or placebo, respectively, for 12 weeks. The use of ACE inhibitors was not allowed

during the treatment period. No patient died in any of the three treatment groups during the 12 weeks of the study. Dickstein et al. (18) recently reported the results of a study very similar in design to the present study. In that trial, patients in functional class III or IV heart failure, most of whom had been previously treated with ACE inhibitors, were randomized to double-blind treatment with 25 mg of losartan every day (n = 52), 50 mg of losartan every day (n = 56) or 10 mg of enalapril twice daily (n = 58) for 8 weeks. All open-label ACE inhibitors were discontinued before randomization, as was done in the present study. During the 8-week treatment period, zero, two and two patients died in the 25-mg losartan, 50-mg losartan and enalapril treatment groups, respectively. Thus, with the exception of the 50-mg losartan treatment group in this study, the mortality rate observed after treatment with 25 mg of losartan every day or 50 mg of losartan every day appears to be low and comparable to the control agent used in the trials. These findings support the interpretation that the mortality difference observed in this study was likely due to chance occurrence related to the use of multiple treatment groups with a small sample size in study design. Moreover, recently published studies further support this interpretation. The Evaluation of Losartan In The Elderly (ELITE) study demonstrated that treatment with losartan was associated with less all-cause mortality than treatment with captopril, a drug known to have survival benefits (19). Similarly, an improvement in survival with losartan of similar magnitude to that seen in the ELITE study has been recently observed in two placebo-controlled, 12-week exercise studies involving 736 patients with symptomatic heart failure (20). In these studies, losartan did not improve treadmill exercise time compared with placebo (the primary end point) but was associated with an unexpected reduction in mortality. All the available data indicate that a trial designed to determine the effects of angiotensin II receptor blockade on mortality in patients with symptomatic heart failure deserves further study and is ethically responsible.

The incidence of nonfatal serious adverse experiences and worsening heart failure symptoms were comparable among the groups. No unexpected serious adverse experiences were reported. Laboratory experience showed no statistically significant differences among the treatment groups, with the exception that the mean changes in serum creatinine from baseline were negligible in both losartan groups, whereas a small increase in creatinine levels was observed in the enalapril group.

Exercise capacity was also evaluated in the study reported by Dickstein et al. (18), which shared a similar study design to that of the present trial. The findings of that study were similar to ours in that no significant intergroup differences were noted with respect to exercise capacity (6-min walk test), clinical status (dyspnea-fatigue index) or incidence of adverse clinical experiences (18). Both of these studies found that losartan was generally well tolerated in the short-term treatment of mild to severe heart failure and that no difference in exercise capacity was observed after treatment with 25 mg of losartan every day, 50 mg of losartan every day or 10 mg of enalapril twice daily for 8 or 12 weeks.

Potential advantages of losartan over nonspecific ACE inhibition. In contrast to losartan, ACE inhibitors interfere with the cleavage not only of angiotensin I, but also of bradykinins, enkephalins and substance P (13,14,21–23). As previously stated, accumulation of these substances is thought to be responsible for the ACE inhibitor–associated side effects of cough and hypotension. In keeping with these observations, a large clinical trial in hypertensive patients recently demonstrated that the incidence of cough with losartan was significantly less than that observed with lisinopril and similar to that noted with hydrochlorothiazide (21). Because all the patients recruited into the current study had previously been successfully treated with an ACE inhibitor (thus eliminating patients intolerant to ACE inhibitors), it is not surprising that the beneficial effect of cough reduction was not evident.

Administration of an ACE inhibitor is associated with a decrease in renal filtration fraction (24). Kon et al. (25) observed a decrease in glomerular filtration fraction with ACE inhibition, which can be prevented by administration of the bradykinin antagonist HOE 140. Bradykinin induced by ACE inhibition could lead to efferent arteriolar dilation and decreased renal perfusion pressure. Losartan, which does not cause bradykinin accumulation, has been shown to raise serum creatinine less than the level previously reported with ACE inhibitors in hypertensive patients (21,26). In addition, hyperkalemia or hyperuricemia have not been found to be a significant problem in trials using losartan (21,26). In this respect, the results of the laboratory data observed in our study support these observations. Specifically, the mean change from baseline in serum creatinine levels was negligible in both losartan groups, whereas an increase was noted in the enalapril group, compared with both baseline values and losartan. In the study of Dickstein et al. (18), which, as mentioned earlier, enrolled patients with severe heart failure, the serum potassium and blood urea nitrogen values, in addition to serum creatinine, also decreased after 8 weeks of treatment in both losartan groups, compared with the enalapril group.

Finally, ACE inhibitor therapy may be associated, at times, with first-dose hypotension (27). This situation is most commonly encountered in patients with hyponatremia, hypovolemia, low baseline blood pressure, renal impairment and high baseline levels of renin or aldosterone (2,3). Potentiation of the vasodilator effects of bradykinins and prostaglandins appears to contribute to the first-dose hypotension associated with ACE inhibitor therapy (28,29). Accordingly, losartan, which does not interfere with the degradation of these peptides, should theoretically result in fewer episodes of first-dose hypotension. In this study, supine and standing blood pressures and pulses were monitored at hourly intervals for 5 h after receiving the initial doses of either losartan (12.5 mg) or enalapril (2.5 mg) and after each titration. Mean changes from baseline for these measurements were small and clinically nonsignificant. No unusual trends associated with a particular treatment were evident from the results.

Study limitations. The fact that all the patients in this study were treated with ACE inhibitors before enrollment intro-

duced a bias into the study because patients who tolerated ACE inhibitor therapy were preselected and the incidence of side effects was minimized (i.e., cough and first-dose hypotension), side effects which might have been otherwise encountered. The long-term effects of the previous ACE inhibitor therapy might have been partially operative for a period after randomization to losartan. Nonetheless, a 12-week trial such as ours should have been of adequate length to detect a deterioration in the clinical status of the patients if treatment with losartan was inefficacious. In previous studies, clinical deterioration became evident 3 and 6 weeks after cessation of therapy with quinapril or enalapril, respectively (30,31). Although the greatest hemodynamic effects were observed with the 50-mg dose of losartan, our study did not clarify the optimal dose of losartan for long-term therapy in patients with heart failure. No obvious differences were noted between the 25- or 50-mg dose of losartan. It is possible that the magnitude of the hemodynamic effect will not translate into differences in clinical outcome, because negative neurohormonal feedback mechanisms may have attenuated potential beneficial responses associated with the greater hemodynamic change. Losartan is a specific angiotensin I receptor blocker and does not inhibit the angiotensin II receptor subtype. Because there is no known physiologic effect of angiotensin II receptor stimulation in adults, the effect of long-term, unopposed angiotensin II receptor stimulation associated with losartan treatment is unknown.

Data do not currently exist on the long-term effects of losartan on clinical end points such as mortality or hospital stays of patients with heart failure. Evaluation of the long-term clinical effects of losartan, alone or in combination with an ACE inhibitor, in patients with heart failure requires further studies.

Conclusions. The results of this study demonstrate that losartan, a novel angiotensin II receptor antagonist, is generally well tolerated in patients with symptomatic heart failure previously treated with ACE inhibitors. Similar effects on functional capacity and clinical status were observed after 12 weeks of once-daily dosing of 25 mg of losartan, or 50 mg of losartan or twice-daily dosing of 10 mg of enalapril. A significant difference in clinical or exercise effects between the 25-mg losartan and 50-mg losartan doses was not observed after 12 weeks of once-daily dosing. This study supports further investigation of losartan for the treatment of patients with heart failure.

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Appendix

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